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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,289	ABARZUA, PATRICIO	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *16,17 and 30* is/are withdrawn from consideration.

5)☒ Claim(s) *31* is/are allowed.

6)☒ Claim(s) *1-14 and 18-29* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

Any rejection not reiterated in this action is hereby withdrawn.

Claims 1-31 are pending. Claims 14, 16, 17 and 30 are non-elected. Claim 15 remains objected to. Claim 31 is allowed.

Claim Rejections - 35 USC § 112

1. Claims 2-11, 25, 27 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what are the metes and bounds of the term "bipolar primer" as used in claim 2. The term appears to be used by the specification in at least two different contexts. In one, the primer is "bipolar, in that it possesses two functionalities separated by a stretch of thymidines (see page 13, lines 5-6)." The rejections of Valimaa in view of Chee alone are made under this definition. However, the specification also notes a second type of P2 which "has reverse polarity 3'-5'-3' (see page 16, lines 8-9). Relying upon this interpretation, a different rejection is made in which Lizardi is also applied.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Valimaa et al (J. Immunol. Methods (1998) 219:131-137).

Valimaa teaches a method of detecting single nucleotide polymorphisms (alleles) (abstract) comprising:

(a) contacting an allele specific oligonucleotide primer with a target polynucleotide, wherein the target polynucleotide has a first portion which is complementary to a second portion on the allele specific oligonucleotide primer under conditions which permit hybridization between the two portions (page 133, column 1, subheading "PCR", where the allele specific primer hybridizes to the target during PCR),

(b) contacting the complex of primer and target nucleic acids with an exonuclease deficient DNA polymerase which extends the primer (see page 133, column 1, subheading "PCR") where the polymerase is Dynazyme II which lacks 3'-5' exonuclease activity (see page 133, column 1, subheading "PCR")

(c) detecting the extended primer (here a PCR product) by removing the target polynucleotide from the complex formed in step (b) by attaching the primer to a solid support composed of plastic (see page 133, subheading "hybridization") and contacting the extended primer (here the PCR product) with a second oligonucleotide which hybridizes to a region of the extended primer (PCR product) which was not in the original primer region (see page 133, column 2, subheading "hybridization"),

(d) detecting the hybridization of the second oligonucleotide with the extended primer whereby said hybridization indicates extension of the primer thereby detecting a

polymorphism in the target polynucleotide (see page 133, column 2 and page 135, figure 2).

Valimaa teaches the use of samples taken directly from human blood which would comprise human genomic DNA.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-14, and 18-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valimaa et al (J. Immunol. Methods (1998) 219:131-137) in view of Chee et al (U.S. Patent 6,355,431).

Valimaa teaches a method of detecting single nucleotide polymorphisms (alleles) (abstract) comprising:

(a) contacting an allele specific oligonucleotide primer with a target polynucleotide, wherein the target polynucleotide has a first portion which is complementary to a second portion on the allele specific oligonucleotide primer under conditions which permit hybridization between the two portions (page 133, column 1, subheading "PCR", where the allele specific primer hybridizes to the target during PCR),

(b) contacting the complex of primer and target nucleic acids with an exonuclease deficient DNA polymerase which extends the primer (see page 133,

column 1, subheading "PCR") where the polymerase is Dynazyme II which lacks 3'-5' exonuclease activity (see page 133, column 1, subheading "PCR")

(c) detecting the extended primer (here a PCR product) by removing the target polynucleotide from the complex formed in step (b) by attaching the primer to a solid support composed of plastic (see page 133, subheading "hybridization") and contacting the extended primer (here the PCR product) with a second oligonucleotide which hybridizes to a region of the extended primer (PCR product) which was not in the original primer region (see page 133, column 2, subheading "hybridization"),

(d) detecting the hybridization of the second oligonucleotide with the extended primer whereby said hybridization indicates extension of the primer thereby detecting a polymorphism in the target polynucleotide (see page 133, column 2 and page 135, figure 2).

Valimaa teaches the use of samples taken directly from human blood which would comprise human genomic DNA.

Valimaa teaches the use of an exonuclease deficient polymerase but not the full list given by Chee. Valimaa does not teach detection using rolling circle amplification.

Chee teaches the desirability of detecting single nucleotide polymorphisms (column 16, lines 25-64) including the use of Klenow, Sequenase, T5 DNA polymerase and Phi29 DNA polymerase among others (column 17, lines 10-12). Chee further teaches detection of the single base extended product using rolling circle amplification with an additional primer that forms a circle (see columns 19-22).

Chee further teaches detection of target sequences in cancer (see column 56, lines 25-29) as well a detection of human clinical samples (which would contain human genomic DNA) for HIV (which would have HIV genomic DNA) (see column 56, lines 35-47).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Valimaa, which is a method in which a mutation is detected by hybridization to a probe with a label, by using the method of Chee who teaches detection of single base extension using a probe with a label where the label enables rolling circle amplification, since the rolling circle amplification of Chee will very significantly increase the signal, making the method of Valimaa more sensitive and more accurate. As Chee notes,

> "The RCA as described herein finds use in allowing highly specific and highly sensitive detection of nucleic acid target sequences. In particular, the method finds use in improving the multiplexing ability of DNA arrays and eliminating costly sample or target preparation. As an example, a substantial savings in cost can be realized by directly analyzing genomic DNA on an array, rather than employing an intermediate PCR amplification step. The method finds use in examining genomic DNA and other samples including mRNA. In addition the RCA finds use in allowing rolling circle amplification products to be easily detected by hybridization to probes in a solid-phase format (e.g. an array of beads). An additional advantage of the RCA is that it provides the capability of multiplex analysis so that large numbers of sequences can be analyzed in parallel. By combining the sensitivity of RCA and parallel detection on arrays, many sequences can be analyzed directly from genomic DNA. (column 22, lines 42-59)".

Thus, an ordinary practitioner would have been motivated to use RCA as a detectable label in the method of Valimaa since RCA saves money, permits multiplexing, increases sensitivity and permits direct detection of genomic DNA.

5. Claims 1-14 and 18-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valimaa et al (J. Immunol. Methods (1998) 219:131-137) in view of Chee et al (U.S. Patent 6,355,431) and further in view of Ishikawa et al (Human Immunology (1995) 42:315-318).

Valimaa in view of Chee teach the limitations of claims 1-14 and 18-25 as discussed above. Valimaa in view of Chee do not teach the use of primers with mismatches near the 3' termini.

Ishikawa teaches that putting mismatches in primers near the 3' termini increases the specificity of amplification (abstract and page 316, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Valimaa in view of Chee for allele specific amplification to use primers which have been modified to improve specificity as taught by Ishikawa since Ishikawa states "the introduction of an additional one-base mismatch is a simple and useful way to improve the specificity (page 316, column 2)". An ordinary practitioner would have been motivated to modify the primers of Valimaa in view of Chee by creating mismatches near the 3' end in order to improve the specificity of the single base extension reaction, thereby improving the quality of the assay and reducing the number of false negative and false positives which would otherwise occur.

6. Claims 1-14, and 18-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valimaa et al (J. Immunol. Methods (1998) 219:131-137) in view of Chee et al (U.S. Patent 6,355,431) and further in view of Lizardi et al (Nature Genetics (1998) 19:22-232) and further in view of Ishikawa et al (Human Immunology (1995) 42:315-318).

Valimaa in view of Chee and further in view of Ishikawa teach the limitations of claims 1-14 and 18-29 as discussed above. Valimaa in view of Chee and further in view of Ishikawa do not teach primers with a 3'-5'-3' polarity.

Lizardi teaches the use of primers with a 3'-5'-3' polarity (see page 228, figure 6) in the RCA method taught by Chee (see page 228).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Valimaa in view of Chee and further in view of Ishikawa to use the 3'-5'-3' polarity primer of Lizardi since Lizardi notes "A larger range of labeling combinations is attainable by RCA-CACHET.(see page 230, column 2)." Lizardi further notes "The single molecule counting approach promises to be both sensitive and linear in its response to target concentration. Individual immunoglobulins can tagged with rolling circle primers can be detected by RCA-CACHET (see page 230, column 2)". Thus, an ordinary practitioner, motivated by Chee as discussed above to apply the RCA method, would have been further motivated by Lizardi to use the modified RCA-CACHET method in order to use a larger range of labeling combinations and increase sensitivity to the point that single molecules may be detectable.

Allowable Subject Matter

7. The elected Restriction subgroup, SEQ ID NO: 13, is novel and unobvious over the cited prior art. While the targeting region to cystic fibrosis is known, the particular sequence with the particular number of T residues attached is not taught by the prior art and is not obvious. Claim 15 is objected to as dependent from a rejected claim but if it was limited to the elected subgroup and rewritten in independent form, the claims would be allowable.

8. Claim 31 is allowed.

9. The following is a statement of reasons for the indication of allowable subject matter: Claim 31 is drawn to an embodiment of the invention which requires the use of SEQ ID NO: 13, which is novel and unobvious over the cited prior art.

Response to Arguments

10. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection, necessitated by Applicant's amendment.

Applicant has one argument which could apply to some of the current rejections. That is that the new claim limitation that the primer is bipolar distinguishes from Chee. However, the specification does not define what constitutes a bipolar primer and the broadest definition in the specification is that "Amplification primer P2 is bifunctional, or bipolar, in that it possesses two functionalities separated by a stretch of thymidines (see page 13, lines 5-6)." Thus, the broadest reading of a bipolar primer is any primer which has a thymidine stretch between two regions. Valimaa shows, in Table I,

primers such as HLA-B-27 3" primer, which have TT in the middle of the oligonucleotide.

For this reason, the additional rejection using Lizardi was applied, in the interest of compact prosecution. It is based upon an alternative interpretation of the term "bipolar primer".

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

February 7, 2003